

**U.S. Department of Energy's
Radiation Health Effects Studies in the Russian Federation**

Proposal Number: 98-0020

Principal Investigator: Guilmette, Raymond A.

Institute: Lovelace Biomedical & Environmental Research Institute

Title of Proposal: Improved Dosimetry and Risk Assessment for Plutonium-induced Lung Disease Using a Microdosimetric Approach

Abstract

The risk of developing radiation-induced cancer and other noncancerous diseases of the lung is currently estimated based on models that use epidemiological data from populations exposed either to relatively uniform, low-LET radiation, or from uranium miners exposed to radon and progeny. Both of these data sets are likely to be inappropriate for predicting the risk of lung disease from inhalation of alpha-emitting radionuclides such as Pu and Am. The most recent respiratory tract dosimetry and risk models have been published by ICRP and NCRP. Although more sophisticated than prior models, they may not be adequate in dealing with the complexities inherent in an exposure regime where nonuniform irradiation of a heterogeneous anatomic structure, the lung, is likely to be the rule rather than the exception. What is needed is a better experimental and theoretical basis for addressing the variabilities in spatial and temporal dose and dose rate on the microscopic scale, and relating these dose metrics to the induction of lesions, particularly at the microscopic scale, in the lung. These are the purposes of this project. The proposed collaboration between scientists at the Branch 1 Center of Biophysics (FIB-1), Ozyorsk, Russia, and the Lovelace Respiratory Research Institute (LRRRI), Albuquerque, NM will make use of a unique resource. A set of about 400 lung specimens fixed in 10% formalin is available from FIB-1. These specimens were obtained from a population of workers at the Mayak Production Association many of whom were exposed to significant quantities of Pu and other alpha-emitting radionuclides during their careers. In Phase I, scientists from LRRRI will join with FIB-1 scientists to evaluate the work and exposure history information, as well as clinical and autopsy data, for the study subjects, and two lung specimens will be identified for analysis. Ideally, one subject will have been a smoker and the other a nonsmoker. The lung specimens will be sampled using classical stereological techniques, embedded in paraffin, sectioned at 5 μ m, and exposed to liquid photographic emulsion for alpha-particle autoradiography. Data will then be collected on the distribution of activity in the sections together with morphometric analysis of the anatomic lung structures in the lung, and correlations will be made between the particle distributions and those structures. These data will allow a preliminary evaluation of the degree of nonuniformity of alpha radiation dose within the lungs of these two subjects. Assuming that the results of the Phase I study are suitable, the Phase II study will then proceed to evaluate the effect of Pu lung burden or dose, and the effect of smoking on the microdistribution and spatial dose patterns from inhaled Pu. Because the inventory of lung samples available in this study consists of those obtained at a minimum of 25 years after the time period over which the highest inhalation exposures likely occurred, the human data will be supplemented with data obtained from experimental animals that inhaled Pu aerosols and were serially killed at early times after exposure. Statistical analysis of these data will provide an improved experimental basis for designing risk models that account for the various degrees of inhomogeneity of lung tissue irradiation from inhaled alpha-particle-emitting radionuclides, and may contribute to our understanding of the relationship between local irradiation and the induction of focal lesions in the lung. This opportunity to improve our understanding of dose-response relationships in humans is unique.

U.S. DEPARTMENT OF ENERGY

FEDERAL ASSISTANCE PROGRAM/PROJECT STATUS REPORT

OMB Burden Disclosure Statement

Public reporting burden for this collection of information is estimated to average 47.5 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden, to Office of Information Resources Management, AD-241.2 - GTN, Paperwork Reduction Project (1910-0400), U.S. Department of Energy, 1000 Independence Avenue, S.W., Washington, DC 20585; and to the Office of Management and Budget (OMB), Paperwork Reduction Project (1910-0400), Washington, DC 20503.

1. Program/Project Identification No. DE-FC03-98EH98032	2. Program/Project Title Improved Dosimetry & Risk Assessment for Plutonium-Induced Lung Disease Using a Microdosimetric Approach	3. Reporting Period 8/15/98 through 11/30/98
4. Name and Address Loveiace Biomedical & Environmental Research Institute P.O. Box 5890 Albuquerque, NM 87185-5890		5. Program/Project Start Date 8/15/98
		6. Completion Date 8/14/03

7. Approach Changes

As a result of discussions with Russian collaborators, the following additions have been made to the original Phase I study design: 1) a third lung specimen chosen to have a relatively low Pu lung content was added to the original two specimens, which are to be a smoker and nonsmoker with high Pu lung contents; 2) to acquaint Russian colleagues with appropriate stereological sampling techniques. Dr. K. Nikula, LLRI, will travel to FIB-1 in January, 1999 and demonstrate the techniques using the three selected lung specimens; 3) to update our Russian colleagues' histotechnical expertise. Dr. O. Zubkhova, FIB-1 pathologist will visit LLRI in March, 1999 to learn sample preparation and autoradiographic methods. These changes can be accommodated within the original Phase I program.

8. Performance Variances, Accomplishments, or Problems

As a result of the LLRI visit to FIB-1, lung tissue paraffin blocks randomly selected from two Mayak workers were transported to LLRI. The tissues were re-embedded in standard paraffin blocks, sectioned at 5 µm, and exposed to Kodak NTB-2 liquid photographic emulsion for times varying from 10 to 40 days. Based on results obtained from the 10-day exposures, it appears that the quality of the tissue fixation and the degree of lung inflation are adequate to allow us to visualize the lung structure and to score the occurrence and location of Pu - particle activity. In the small number of slides examined to date, both single tracks and Pu stars, indicating the presence of intact Pu particles were seen. In one section containing intrapulmonary lymphoid tissue, at least 60 Pu particles could be visualized. During this quarter, Dr. Nikula attended the International Society of Stereology, American Stereology Course, a shop for practicing stereologists, and used the opportunity to "fine tune" our sampling design by soliciting input from the attending staff and participants. As a result, we are confident in our ability to sample the Russian lung specimens according to robust stereological methods, and expect to obtain data that will allow us to quantitate the retention of Pu activity in the various lung compartments, and to estimate local radiation doses to those compartments.

9. Open Items

☒ None

10. Status Assessment and Forecast

The Phase I project is on schedule. Dr. Nikula will be traveling to Ozersk during the second week in January to instruct the Russians in proper stereological sampling technique, and will return to LLRI with the paraffin blocks from the three selected lung specimens. Autoradiography will then be done at LLRI. Dr. Zubkhova will be trained, and autoradiographic data will be collected and analyzed at LLRI.

☐ No deviation from Plan is Expected

11. Description of Attachments

☒ None

Signature of Recipient and Date

13. Signature of U.S. Department of Energy (DOE) Reviewing Representative and Date

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Protocol
of co-ordination of the program of research work on project DOE N 03-98EH98032
"Improved dosimetry and risk assessment for plutonium-induced lung disease using a
microdosimetric approach".

The participants of the meeting held on September 2, 1998.

- From the American side: Dr. R. Guilmette, scientific leader of the project; Dr. K.J. Nikula, pathologist.
- From the Russian side: Dr. S. Romanov, FIB-1 director, scientific leader of the project; Dr. A. Niphatov, pathologist; Dr. O. Zubkova, pathologist; Dr. N. Koshurnikova, principal researcher at the epidemiology laboratory; Dr. N. Shilnikova, epidemiologist.

At the meeting a proposal for the project prepared by the American collaborators was discussed. Some comments were made, and the participants agreed to make some corrections in the text of the document.


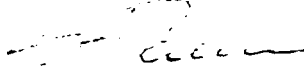
The parties have come to the mutual agreement, that the principal purpose of the pilot project is to determine, whether or not it is feasible to use archival autopsy materials accumulated at FIB-1, for studying microdistribution of plutonium in the lung using histoautoradiography method.

To achieve this principal purpose, the parties have outlined the following stages of work:

1. Acquaintance with methods used at FIB-1 and LRRJ for sampling of the lung tissue and preparing histoautoradiograms, and co-ordination of these methods. October-December, 1998.
2. Sampling of the lung tissue using coordinated method, and preparing paraffin embedded material. January, 1999. This work will be conducted at FIB-1 with participation of an American specialist.
3. Histoautoradiograms will be prepared at LRRJ upon return from FIB-1. January-February, 1998.
4. Russian specialist will visit LRRJ to participate in stereologic analysis of developed histoautoradiograms. Specialist will also prepare additional histoautoradiograms of separate material for teaching purposes. This work will be conducted at LRRJ with participation of the Russian specialist. February-March, 1999.
5. Stereologic analysis may be continued at LRRJ. Results will be analyzed jointly. A feasibility report and project summary will be prepared by investigators for DOE. May, 1999.
6. Joint analysis of the data obtained in the course of the project will be completed and a final report on the pilot project prepared. The proposal for a long-term joint project (Phase 2) will also be prepared. July-August, 1999.

The parties have come to the conclusion, that this plan is only relevant to the fulfillment of the pilot project. If the pilot project is completed successfully, and it is decided, that a long-term project is possible, then it is intended that all the work on sampling, and preparation of autoradiograms will be done at FIB-1; analysis will be conducted in parallel at FIB-1 and LRRJ. A special laboratory will be created at FIB-1 for conducting this work.

Scientific leaders of the project:

 R. Guilmette
 S. Romanov